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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/124,485	07/29/1998	NICHOLAS MARK ANSTEY	73-97	6763

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/124,485	ANSTEY ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33,38,40,41,46 and 48* is/are pending in the application.

4a) Of the above claim(s) *27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 40-41, 46, 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and declarations filed on 10/17/2004 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claim 1-26, 34-37, 39, 42-45, 47 are cancelled.
2. Claim 48 is added to the instant application.
3. Currently, claims 38, 40-41, 46, 48 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 38, 40-41, 46, 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The current case recites a method for the prophylaxis ***(prevention)*** or treatment of infection by a *Plasmodium* species in a non-mammal, i.e. human, by administering an agent capable of increasing the level of nitric oxide in the body. (See claim 38)(empha The *Plasmodium* infected disease is particularly on malaria. Although applicant discloses general protocols in selecting patients, dietary control, sample collection, nitrate administering and measuring NO level, statistically analysis method, readjusting confounding factors, such as renal failure. (See examples 1-21) The results in this instant application do not provide sufficient information or guidance to one ordinary skilled in the art to use or conduct the recited method in achieving the claimed effect.

Adequate clinical model

Applicant provides data with respect to the inhibition of cytoaherence to either RBC or to C32 melanoma cells. (See Figure 1 and 2) The inhibition of cytoadherence has been shown "reduces the *likelihood* of infection of severe infection by Plasmodium species." (See page 14, last paragraph) Those data represent in vitro correlation between the different Plasodium strains (Figure 1) and the level of S-nitrosylation on RBC (Figure 2). Applicant asserts that the data support the notion that *RSNO treatment of parasitised red blood cells* inhibits cytoadherence to C32 cells. (See page 34, line 27-28) (emphasis added) This example merely shows an in vitro treatment on parasitised red blood cells, not an in vivo treatment on human subjects as recited in the current claim 38-39. There is no causal-effect relationship, i.e. decrease the severity of malaria disease. The data merely provides observation of the treatment on parasitised red blood cells with the RSNO.

The issue is that whether this in vitro model is an adequate model to reflect the effectiveness of an in vivo treatment on human. Alternatively, at issue is whether or not the claimed therapeutic method would function to treat human infected by Plasodium. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area, the more specific enablement is necessary in order to satisfy the statutory requirement of 35 U.S.C §112, first paragraph. Since no animal/or human were used as model system to treat Plasodium infected disease, it is not

clear how reliable one skilled in the art may depend on the instant claimed method. The specification does not teach how to extrapolate data obtained from in vitro assays to the development of effective in vivo human treatment, commensurate in scope with the claimed invention. In view of the aforementioned lack of predictability in the art, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the recited method and absent working examples.

Prophylaxis (prevention)

With respect to prophylaxis (*prevention*), the data (Figure 1 and 2) do not provide sufficient instructions and information to one skilled in the art to perform the recited administering NO agents to achieve the preventive goal. Factors, including metabolism, site-administering, effective dosages...etc, are confounding parameters in evaluation of the effectiveness of the prevention. The current in vitro data do not support the notion that the administering in vivo would, in fact, "prevent" the occurrence of malaria disease (emphasis added). Furthermore, the specification does not disclose what are the criteria for one skilled in the art to evaluate the effectiveness of prevention. Treatment relates to some pathological state already occurred, whereas prevention refers to inhibit occurrence of that pathological state in a healthy human. It is unclear how reliable these in vitro data can adequately reflect the degree of in vivo prevention. Based on the predictability on the aspect of recited prophylaxis (*prevention*), it is inevitable that undue experimentation would impose to one skilled in the art to ascertain the effective way, manner or performance to use this claimed method.

Response to Applicant's Arguments

3. The rejections of previous claims 38-43, 45-47 under 35 USC 112, first paragraph, scope of enablement, are withdrawn.

Applicant argues that administering compounds to human subjects is within ordinary skilled in the art. Applicant's declarations with references (Boger et al. and Morris et al.) have been considered but are not material to examiner's rejection. Examiner did not raise the question that "the present specification does not describe the details of how to administer the compounds contemplated by the claim" as alleged by the applicant (See page 5, Remarks). Therefore, there is no need to address this issue.

In vitro model

Applicant's declarations present numerous references, including post-filing date art, attempting to show support of enablement for the instant claims (See declaration Exhibits, A- I). The main issue is that whether applicant's in vitro experimental data can be extrapolated into a reliable in vivo model. Most importantly, with the in vitro disclosure in the specification, whether one ordinary skilled in the art can achieve the purported purpose, namely prophylax (prevention) or treatment of malaria by administering agents to patients to increase nitric oxide levels.

Examiner had indicated in this Office Action the insufficiency of the existing in vitro data to reflect to an in vivo condition. The data merely provides observation of the treatment on parasitised red blood cells with the RSNO. It requires a leap of faith to ascertain the efficacy of the in vitro observation to the in vivo treatment. Applicant submitted his own post-filing date publication and argues that the claimed methods are applicable to the treatment of malaria disease (See page 7, first paragraph; See Exhibit I, *Anstey et al. Am. J. of Tropical Medicine and Hygiene (2002) 67(2): abst. 515*). In review of this publication, no data or results have been shown to the treatment or prevention of malaria by administering agents to increase nitric oxide levels (emphasis added). The conclusion of this publication is that there exists an inverse relationship between Plasmodium malaria and the level of nitric oxide in the patients. Furthermore, another applicant's own post-filing date reference also implies uncertainty with respect to the treatment or prevention of the current purported method (See Exhibit A, The *LANCBT 2003 Vol. 361: 676*). Applicant states that "[w]hether or not severe disease is caused

by, or results from, hypoargininsemia is *unclear*" (See page 677, right column, fourth paragraph)(emphasis added). Additionally, applicant concludes that "[c]linical trials are warranted to ascertain whether or not correction of L-arginine deficiency provides adjunctive prophylactic and therapeutic benefit to malaria" (See page 678, left column, last paragraph)(emphasis added). In another word, nearly 5- year after filing this application (filing date 7/9/1998), there is still some uncertainty concerning the in vivo effects, i.e. prevention and treatment. Accordingly, the enablement rejection under 35 USC 112, first paragraph, is deemed proper.

Conclusion

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

December 1, 2004

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

12/10/04